X-linked infantile spasm syndrome

X-linked infantile spasm syndrome is a seizure disorder characterized by a type of seizure known as infantile spasms. The spasms usually appear before the age of 1. Several types of spasms have been described, but the most commonly reported involves bending at the waist and neck with extension of the arms and legs (sometimes called a jackknife spasm). Each spasm lasts only seconds, but they occur in clusters several minutes long. Although individuals are not usually affected while they are sleeping, the spasms commonly occur just after awakening. Infantile spasms usually disappear by age 5, but many children then develop other types of seizures that recur throughout their lives.

Most babies with X-linked infantile spasm syndrome have characteristic results on an electroencephalogram (EEG), a test used to measure the electrical activity of the brain. The EEG of these individuals typically shows an irregular pattern known as hypsarrhythmia, and this finding can help differentiate infantile spasms from other types of seizures.

Because of the recurrent seizures, babies with X-linked infantile spasm syndrome stop developing normally and begin to lose skills they have acquired (developmental regression), such as sitting, rolling over, and babbling. Subsequently, development in affected children is delayed. Most affected individuals also have intellectual disability throughout their lives.

Frequency

Infantile spasms are estimated to affect 1 to 1.6 in 100,000 individuals. This estimate includes X-linked infantile spasm syndrome as well as infantile spasms that have other causes.

Genetic Changes

X-linked infantile spasm syndrome is caused by mutations in either the *ARX* gene or the *CDKL5* gene. The proteins produced from these genes play a role in the normal functioning of the brain. The ARX protein is involved in the regulation of other genes that contribute to brain development. The CDKL5 protein is thought to regulate the activity of at least one protein that is critical for normal brain function. Researchers are working to determine how mutations in either of these genes lead to seizures and intellectual disability.

Infantile spasms can have nongenetic causes, such as brain malformations, other disorders that affect brain function, or brain damage. In addition, changes in genes that are not located on the X chromosome cause infantile spasms in rare cases.

Inheritance Pattern

X-linked infantile spasm syndrome can have different inheritance patterns depending on the genetic cause.

When caused by mutations in the *ARX* gene, this condition is inherited in an X-linked recessive pattern. The *ARX* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. Usually in females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. However, in some instances, one altered copy of the *ARX* gene is sufficient because the X chromosome with the normal copy of the *ARX* gene is turned off through a process called X-inactivation. Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. Usually X-inactivation occurs randomly, such that each X chromosome is active in about half of the body cells. Sometimes X-inactivation is not random, and one X chromosome is active in more than half of cells. When X-inactivation does not occur randomly, it is called skewed X-inactivation. Some *ARX* gene mutations may be associated with skewed X-inactivation, which results in the inactivation of the X chromosome with the normal copy of the *ARX* gene in most cells of the body. This skewed X-inactivation causes the chromosome with the mutated *ARX* gene to be expressed in more than half of cells, causing X-linked infantile spasm syndrome.

When caused by mutations in the *CDKL5* gene, this condition is thought to have an X-linked dominant inheritance pattern. The *CDKL5* gene is also located on the X chromosome, making this condition X-linked. The inheritance is dominant because one copy of the altered gene in each cell is sufficient to cause the condition in both males and females.

X-linked infantile spasm syndrome caused by *CDKL5* gene mutations usually occurs in individuals with no history of the disorder in their family. These mutations likely occur in early embryonic development (called de novo mutations). Because males have only one X chromosome, X-linked dominant disorders are often more severe in males than in females. Male fetuses with *CDKL5*-related X-linked infantile spasm syndrome may not survive to birth, so more females are diagnosed with the condition. In females, the distribution of active and inactive X chromosomes due to X-inactivation may affect whether a woman develops the condition or the severity of the signs and symptoms. Generally, the larger the proportion of active X chromosomes that contain the mutated *CDKL5* gene, the more severe the signs and symptoms of the condition are.

A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- early infantile epileptic encephalopathy
- infantile epileptic-dyskinetic encephalopathy
- ISSX
- X-linked West syndrome

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Early infantile epileptic encephalopathy 2
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1839333/
- Genetic Testing Registry: West syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0037769/

Other Diagnosis and Management Resources

- Child Neurology Foundation
  http://www.childneurologyfoundation.org/disorders/infantile-spasms/
- National Organization for Rare Disorders (NORD) Physician Guide
  http://nordphysicianguides.org/infantile-spasms/

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html
- Health Topic: Epilepsy
  https://medlineplus.gov/epilepsy.html

Genetic and Rare Diseases Information Center

- West syndrome
  https://rarediseases.info.nih.gov/diseases/7887/west-syndrome

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Infantile Spasms Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Infantile-Spasms-Information-Page

Educational Resources

- Centers for Disease Control and Prevention: Intellectual Disability Fact Sheet
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/IntellectualDisability.pdf
- Orphanet: West syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=3451

Patient Support and Advocacy Resources

- Child Neurology Foundation
  http://www.childneurologyfoundation.org/disorders/infantile-spasms/
- Citizens United for Research in Epilepsy (CURE)
  http://www.cureepilepsy.org/home.asp
- ICE Epilepsy Alliance
  http://www.ice-epilepsy.org/
- National Organization for Rare Disorders (NORD): West Syndrome
  https://rarediseases.org/rare-diseases/west-syndrome/
- University of Kansas Medical Center Resource List: Developmental Delay
  http://www.kumc.edu/gec/support/devdelay.html

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22X-linked+infantile+spasm+syndrome%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28x-linked+infantile+spasm+syndrome%5BTIAB%5D%29+OR+%28early+infantile+epileptic+encephalopathy%5BTIAB%5D%29+OR+%28infantile+epileptic-dyskinetic+encephalopathy%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+2520+days%22%5Bdp%5D

OMIM

- EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 1
  http://omim.org/entry/308350
- EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 2
  http://omim.org/entry/300672

Sources for This Summary

- Hrachovy RA, Frost JD Jr. Infantile epileptic encephalopathy with hypsarrhythmia (infantile spasms/West syndrome). J Clin Neurophysiol. 2003 Nov-Dec;20(6):408-25. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14734931
- Kato M. A new paradigm for West syndrome based on molecular and cell biology. Epilepsy Res. 2006 Aug;70 Suppl 1:S87-95. Epub 2006 Jun 23. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16806828
- Kossoff EH. Infantile spasms. Neurologist. 2010 Mar;16(2):69-75. doi: 10.1097/NRL.0b013e3181d1416c. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20220440
- Olivetti PR, Noebels JL. Interneuron, interrupted: molecular pathogenesis of ARX mutations and X-linked infantile spasms. Curr Opin Neurobiol. 2012 Oct;22(5):859-65. doi: 10.1016/j.conb.2012.04.006. Epub 2012 May 5. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22565167
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437236/
- Sartori S, Polli R, Bettella E, Rossato S, Andreoli W, Vecchi M, Giordano L, Accorsi P, Di Rosa G, Toldo I, Zamponi N, Darra F, Dalla Bernardina B, Perilongo G, Boniver C, Murgia A. Pathogenic role of the X-linked cyclin-dependent kinase-like 5 and aristaless-related homeobox genes in epileptic encephalopathy of unknown etiology with onset in the first year of life. J Child Neurol. 2011 Jun;26(6):683-91. doi: 10.1177/0883073810387827. Epub 2011 Apr 11.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21482751

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